



Biopharmaceutics Modelling as a Fundamental Tool to Support Accelerated Access

Executive Summary

The acceleration of clinical development programs leads to the compression of the time available for the technical development of the Medicinal Product. Under these circumstances, CMC changes and bioequivalence studies to underwrite these, may affect the ability to rapidly deliver innovative medicines to the patients.

A deep understanding of fundamental biopharmaceutics properties of the active substance and product and the application of biopharmaceutics models beyond the BCS-based biowaivers are powerful tools in the acceleration of development programs.

Through drug development, commercialization and post-approval, a number of optimisations of the formulation, manufacturing process and scale and drug substance characteristics may require demonstration of equivalence of the product before and after change. Late stage changes in development, through launch and product life cycle may be particularly frequent in accelerated development programs to optimise the product and control strategy, guarantee a sustainable supply chain and improve patient convenience and adherence. Thus, managing such changes in an effective and efficient manner can be of significant importance for such accelerated programs.

Using a combination of advanced bio-relevant *in vitro* systems and *in silico* Physiologically Based Biopharmaceutics Modeling (PBBM), in combination with agile and information-rich clinical study designs will enable rapid development and change management of drug products with optimal performance. These tools can be applied, through development, commercialization and post-approval, to drug substance property and formulation selection, optimisation and change management; process optimisation and scale-up.

While biopharmaceutics models are already used in the pharmaceutical industry to accelerate internal decision making for the design and selection of clinical and market formulations, widening the understanding and regulatory acceptability of such approaches constitutes a significant opportunity to accelerate the development of high-quality medicines and early patient access to new medicines.

Introduction

In response to the need to accelerate development of high-quality medicines that meet unmet medical needs, regulators in various jurisdictions have introduced new regulatory approaches with focus on faster translation of scientific breakthroughs to products for patients.

In the USA the 'Breakthrough Therapy Act' was signed into law on 9 July 2012.

FDA issued a Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics in May 2014 and a draft Guidance for Industry FDA Rare Diseases Common Issues in Drug Development in February 2019.

In Europe, after the initial Medicines Adaptive Pathways to Patients (MAPPs) program in 2012, EMA introduced two new regulatory approaches: Adaptive Pathways (AP) and Priority Medicines (PRIME) in 2016.

In Japan, the SAKIGAKE Designation System for early product review was introduced in 2015 aiming at earlier marketing authorizations for innovative pharmaceutical products, medical devices and regenerative medicines.

These schemes are based on one or more of the following elements: enhanced interaction and early dialogue with developers, expedited review, application of surrogate endpoints and conditional approval for a restricted patient population.

The acceleration of clinical development programs leads to the compression of the time available for the technical development of the Drug Substance and Drug Product. In a traditional drug development program, the design and optimisation of the formulation for pivotal clinical studies and commercial supply would typically commence (at the earliest) in parallel with Phase 2 studies, building on learning from the first-in-human clinical data, with ample time for bridging studies to be performed off the critical path and ideally prior to the start of pivotal clinical trials. In contrast, under the accelerated development paradigm, Phase 2 clinical studies provide pivotal safety and efficacy data for registration. The drug product dosed in these studies becomes the reference product to which any subsequent drug product improvements must be compared according to the regulatory guidelines covering pivotal formulation comparisons (i.e. bioequivalence and biowaiver guidelines), which can restrict the scope of changes made. A different approach to formulation development, optimisation and bridging is therefore needed for accelerated developments, to avoid the risk of being constrained to launch a non-optimised early formulation and the associated drug delivery profile, and to ensure that patients can benefit from drug products which are optimised based on emerging clinical knowledge and understanding from human studies.

The impact of these issues on the patient and healthcare system is eloquently described by Herbrink et al. (2017)¹, for Signal Transduction Inhibitors in the oncology setting. The authors cite the imbalance between the highly developed pharmacology of this class of drugs, and the frequently non-optimal formulations in which they are delivered. The following specific impacts are highlighted, which could be ameliorated or avoided through more optimal formulation development:

- Waste of drug substance due to low bioavailability, meaning that a high percentage of the drug substance (which can form a significant part of the product cost) is excreted without ever being absorbed
- Potentially insufficient efficacy over time, due to insufficient and/or variable bioavailability.
- Significant alterations in bioavailability with food and co-medications, leading to dosing constraints.
- Increased need for therapeutic drug monitoring in the clinical setting to avoid inadequate exposure due to the high inter-patient variability, leading to increased healthcare costs (the authors cite a need for dose correction due to inadequate exposure in 25% of patients in their institution).

Since limited mention of CMC aspects for those accelerated access approaches was available in the public domain, the pharmaceutical industry has been pursuing interaction with the regulators to discuss options that may be acceptable to Regulatory Authorities to support accelerated access to medicines by reducing the overall time required to develop a new product without compromising quality and safety. In December 2017, after consultation with EMA, EFPIA-EBE published a White Paper² outlining options for the acceleration of CMC development. The White Paper underlines principles and illustrative examples of CMC approaches to development and manufacturing which a company may undertake to facilitate accelerated review or early access. Areas of opportunity are identified in the White Paper such as process validation, stability, control strategy, formulation and manufacturing process development and use of biopharmaceutics models.

In November 2018, EMA and FDA jointly organized a stakeholder workshop on support to quality development in early access approaches such as Priority Medicines and Breakthrough Therapies. Most focus areas described in the White Paper were addressed during the workshop, however, biopharmaceutics modeling could not be discussed as it is a topic which goes beyond the CMC area and requires PK expertise which was not part of the workshop. This highlights the need for experts in quality and PK to work together on the development of Biopharmaceutics modeling tools.

Industry believes that a deep understanding of fundamental biopharmaceutics properties of the active substance and product and the application of biopharmaceutics models are powerful tools in the acceleration of development programs.

Therefore, this White Paper has been developed to illustrate some opportunities and applications of Biopharmaceutics models to support accelerated access to medicines by reducing the overall time required to develop a robust high-quality drug product with the desired clinical performance. The use of Biopharmaceutics models may also lead to a decreased need for *in vivo* data avoiding exposure of healthy volunteers during the execution of BE studies. Moreover, oncology is an area with a considerable number of medicines targeting unmet medical needs and being developed under accelerated programs. Often, due to the toxicological profile of these compounds, BE studies cannot be conducted in healthy volunteers. This requires studies to be conducted on patients, which makes recruitment slower, and the study conduct more complex. These kinds of compounds, which are likely candidates for accelerated access, necessitate a greater reliance on predictive tools.

Regulatory Considerations

While biopharmaceutics models are widely used in the pharmaceutical industry to accelerate internal decision making for the design and selection of clinical and market formulations, regulatory applications to enable early access to new drugs have been limited so far. The establishment of a framework to be able to utilize information from biopharmaceutics models in a regulatory context could support acceleration of patient access to new medicines without compromise for the patients.

Through drug development, commercialization and post-approval, a number of optimisations of the formulation, manufacturing process and scale and drug substance characteristics may require demonstration of equivalence of the product before and after change. Late stage changes in development, through launch and product life cycle may be particularly frequent in accelerated development programs to optimise the control strategy, guarantee a sustainable supply chain and improve patient convenience and adherence.

To define whether equivalence can be demonstrated with *in vitro* data, reference is typically made to guidelines^{3 4 5} describing the conditions and requirements for the application of biowaivers based on the Biopharmaceutical Classification System.

A biowaiver is generally accepted for immediate release drug products, which contain drug substance of BCS Class I or III and fulfil the following conditions:

- BCS Class I:
 - Demonstrated very rapid ($\geq 85\%$ within 15 min) or rapid ($\geq 85\%$ within 30 min) *in vitro* dissolution characteristics and similar *in vitro* dissolution characteristics of the test and reference products under all the defined conditions
 - Excipients that may affect bioavailability are qualitatively and quantitatively the same
- BCS Class III:
 - Demonstrated very rapid ($>85\%$ within 15 min) *in vitro* dissolution characteristics of the test and reference product
 - Excipients that may affect bioavailability are qualitatively and quantitatively the same and other excipients are qualitatively the same and quantitatively very similar

Dissolution is performed within the pH range 1 – 6.8 (at least 1.2, 4.5 and 6.8)

The same principles are described in the ICH M9 Guideline 'Biopharmaceutics Classification System-based Biowaivers'⁶.

Whereas the application of this widely recognized classification system supports the use of biowaivers in a number of situations, many drug substances are BCS Class II and IV or, if BCS Class I or III, do not fulfil the condition of being rapidly dissolving and/or meet the excipient limitations. However, the scientific basis for understanding the risks of bio-inequivalence is rapidly evolving, and new biorelevant *in vitro* and *in silico* tools, often specifically targeted at the scenarios not covered by BCS biowaivers, are emerging. For instance, the EU funded IMI OrBiTo project (ORal Biopharmaceutics TOols), has promoted through industry/academia collaboration a more robust set of biorelevant *in vitro* tools for the prediction of human *in vivo* performance.^{7 8} Similarly, it has sought to determine best practice in the use of Physiologically Based Biopharmaceutics Modeling (PBBM) for the prediction of human pharmacokinetics including the impact of formulation change⁹. The IMI OrBiTo collaboration also actively engaged with regulatory agencies in mapping potential future strategies, for instance, as envisaged from the output of the collaboration's 2015 open meeting on *In vivo* Predictive Dissolution (IPD) and biopharmaceutical modeling and simulation in a regulatory context.¹⁰ There is an opportunity to move beyond traditional BCS thinking to understand *in vitro/in vivo* relationship on a product-specific basis, using the tools described later in this White Paper to enable the establishment of clinically relevant *in vitro* tests and acceptance criteria. This, in combination with *in silico* modeling, can be used to facilitate rapid product and process establishment, with optimisation and scale up based on knowledge of the potential *in vivo* impact of any changes, and ultimately to define the control strategy to ensure that drug product of suitable clinical quality is always delivered.

Opportunities

Using a combination of advanced bio-relevant *in vitro* systems and *in silico* Physiologically Based Pharmacokinetic Modeling (PBBM), in combination with agile and information-rich clinical study designs will enable rapid development of drug products with optimal performance and facilitate product and process optimisation during the life cycle.

Advanced *in vitro* dissolution models can be used to predict *in vivo* dissolution and streamline selection of API solid form and formulations. Advanced *in silico* PBB models can be used to reduce uncertainty around likely clinical performance and inform formulation selection and Phase 1 study design. Investing in formulation understanding studies earlier in development will streamline later development and formulation bridging approaches and build confidence in the *in vitro* and *in silico* models. The use of flexible adaptive designs for clinical formulation performance studies can facilitate rapid formulation selection and development by enabling teams to respond to the data from each study cohort to inform the design of the next; whilst the use of the IV micro-tracer technique (where a concomitant intravenous radio-labeled micro-dose is given with an oral dose) enables generation of intravenous PK data much earlier in development, significantly reducing the uncertainty around *in silico* pharmacokinetic predictions.

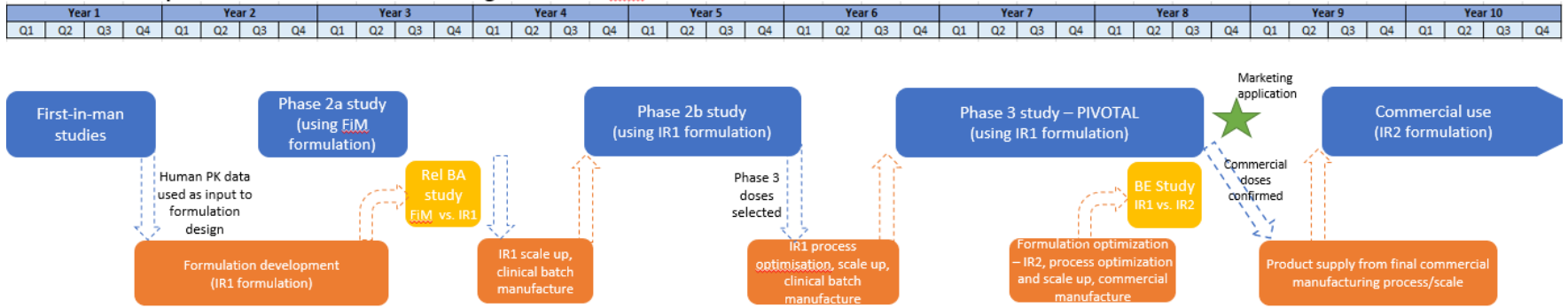
These approaches can therefore enable rapid development of drug products with optimal performance and can be applied to drug substance property and formulation selection, optimisation and bridging of changes; process optimisation and scale-up. They can be applied through development, commercialization and post-approval. Examples of the opportunities offered include:

- Identifying and understanding critical factors for *in vivo* performance
- Faster selection of the commercial formulation
- More predictable BE study outcomes
- Reducing the need for critical-path BE studies (typically taking 6+ months) to support formulation optimisation and other changes required during fast moving projects (e.g. to particle size, manufacturing process, scale-up)
- Establishment of clinically relevant dissolution acceptance criteria without BE studies and unnecessary exposure of healthy volunteers
- Support rapid scale-up and supply chain robustness, corroborate the overall control strategy and guarantee supply continuity for these essential products minimizing the risk of supply shortage
- Anticipate food effect at early development stage

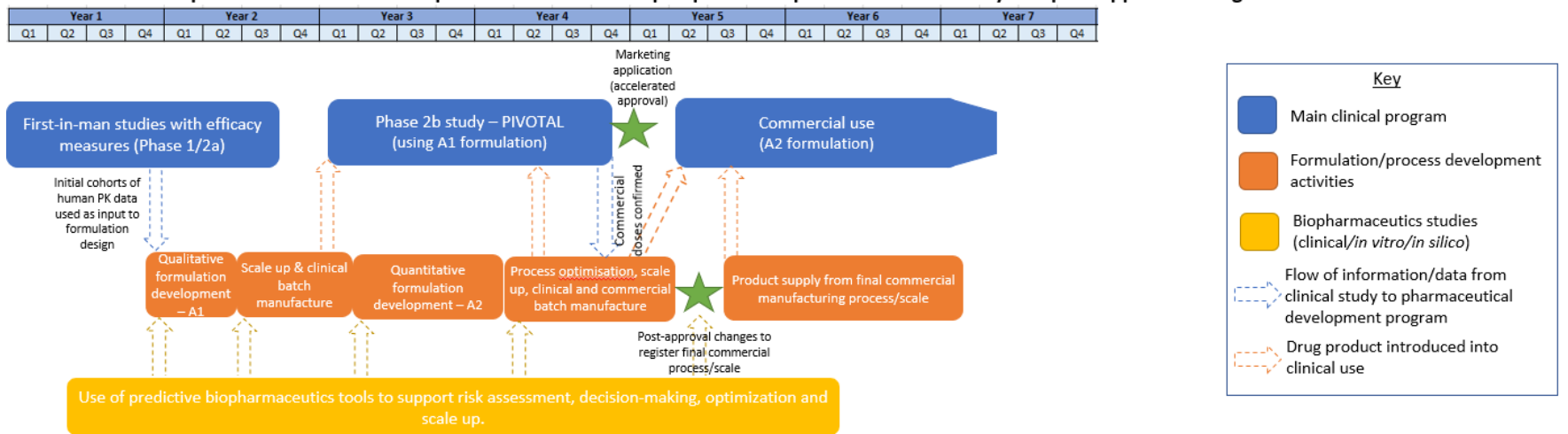
Figure 1 compares a typical drug development program vs. an accelerated development, illustrating the significantly compressed timelines for drug product development and formulation bridging in the accelerated scenario. For the standard development, first-in-human and Phase 2a studies are performed with a drug-in-capsule formulation. An IR tablet (IR1) is developed for Phase 2b and Phase 3 studies. The IR1 formulation is further optimised for commercial use, in parallel with Phase 3: drug loading is increased, minor qualitative excipient changes are made (beyond SUPAC Level 2), and the colour of the non-functional film coat is changed (IR2 formulation). For the accelerated development, The Phase 2b study becomes pivotal registration data. An initial IR tablet formulation (A1) is dosed at the start of the pivotal study, and the qualitative composition is optimised in parallel with the pivotal study (A2 formulation). Some batches of the A2 formulation are included in the pivotal study, and bridging is supported using predictive *in vitro* and *in silico* models. Further process optimisation and scale-up is conducted and registered as a post-approval change.

Figure 1: Comparison of a typical drug development program vs. an accelerated development program

Standard development with two formulation changes between FiM and commercial



Accelerated development with formulation optimization and scale up in parallel to pivotal Phase 2b study and post-approval changes



Applications of Biopharmaceutics Models

This section illustrates examples of applications of various Biopharmaceutics models such as bio-relevant *in vitro* systems and tools, *in silico* modeling of *in vitro* tests, *in silico* physiologically based biopharmaceutics models, and agile and information rich *in vivo* study designs. The application of these tools can support accelerated access and sustained supply of medicines developed under accelerated programs.

Bio-relevant *in vitro* Systems/Tools

Emerging biorelevant *in vitro* tools can be used as a stand-alone model, with the biorelevant *in vitro* tool replacing more conventional dissolution in a traditional IVIVC. Recently, the IMI OrBiTo collaboration produced a decision tree to guide scientists through some of the many different options for biorelevant dissolution.¹¹

Biorelevant dissolution may be used in one of two complementary ways with PBB models.

- 1) To independently confirm that the key sensitivities are correctly identified, and the range of *in vivo* dissolution profiles estimated by a PBB model are realistic
- 2) To generate more reliable model input data, which can then be incorporated into the PBB model.

Biorelevant *in vitro* tools vary in their complexity, with the degree of complexity needed being dependent on the drug and product properties and the purpose of the test. Examples of complex models which holistically incorporate secretory, dynamic and motility-related properties of significance for upper GI tract behavior of drugs and dosage forms that are challenging to mimic in simpler tests include:

- TIM-1 /TinyTIM (TIM Company)¹²
- DGM/Model Gut (Bioneer/IFR)¹³
- The BioGIT model (developed by the University of Athens)¹⁴
- The GIS model (developed/optimised by the University of Michigan)¹⁵
- Further information on the background and the development of these tools can be found in the appropriate references (see reference section). This is not an exhaustive list, and other complex *in vitro* tools have been reported in the literature.

Examples of simpler biorelevant dissolution tools, which focus on one or two parameters important for specific drugs/formulation types include:

- The use of biorelevant media in USP II paddle apparatus, optionally with a media addition step to mimic stomach to intestinal transfer¹⁶
- The use of biorelevant media in the USP III & IV apparatus for improved *in vitro* dissolution of extended/modified release dosage forms¹⁷
- The use of biorelevant media in simple gastric to intestinal transfer experiments to measure precipitation kinetics¹⁸

These tools have important roles to play in accelerated development and in lifecycle management, to support formulation design and optimization, predict likely product performance *in vivo*, understand biopharmaceutics risk and potential sources of variability in the patient population, and to assess the potential *in vivo* impact of changes made to API and formulation characteristics and manufacturing process.

In silico modelling of *in vitro* tests

Recognition of the need for mechanistic modelling of *in vitro* experiments to extract optimal parameters for use in physiologically based biopharmaceutics models is evident through a number of published examples (Pathak, 2017, Basu, 2019)^{19 20}. The combination of increasingly sophisticated and biorelevant *in vitro* experiments with mechanistic modeling should lead to improved ability to link product characteristics to clinical performance and enable industry and regulators to achieve more efficient, effective and clinically-relevant development throughout the lifecycle of the drug product (Suarez-Sharp et al 2018, Pepin et al, 2020)^{21 22}. Commercial suppliers of the most commonly used PBB platforms now supply tools for the modelling of *in vitro* experiments. Commonly used examples include the SIVA toolkit (<https://www.certara.com/software-old/physiologically-based-pharmacokinetic-modeling-and-simulation/siva/>), which is designed to be used with the SimCYP PBPK simulator and the DDDPlus²³ software (<https://www.simulations-plus.com/software/dddplus/>), which is marketed by Simulations Plus for use with GastroPlus.

General considerations on Pharmaceutically Based Biopharmaceutics Modeling

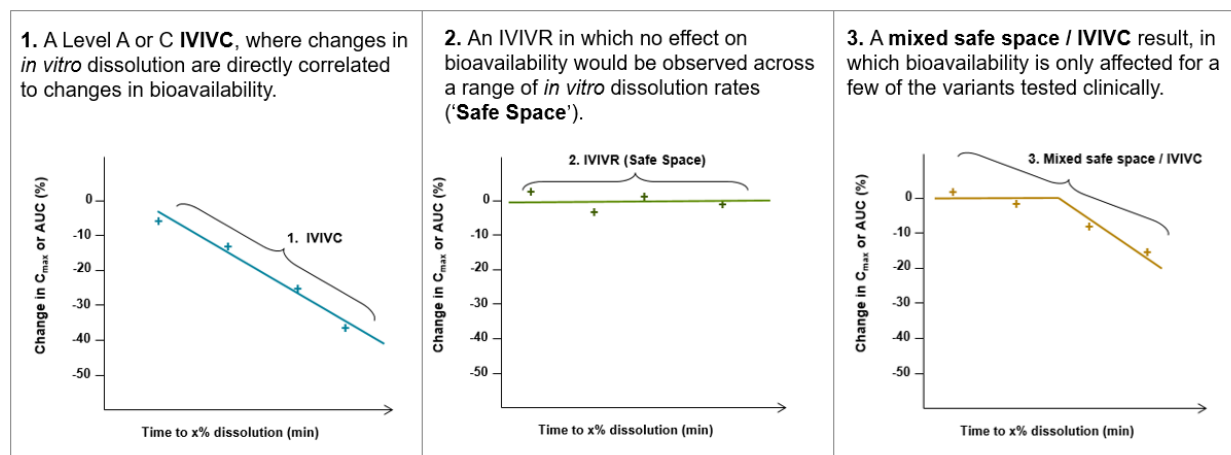
In accelerated development scenarios, where only limited *in vivo* data are initially available, bottom-up approaches for PBB model development based on accurate experimental *in vitro* or *in silico* input data are particularly important. PBBM-based strategies for prediction of human pharmacokinetics are often employed (Jones, 2006. Miller, 2019)^{24 25 26} and pre-clinical animal pharmacokinetic data may be leveraged together with the human relevant *in vitro* data. In addition, data obtained from animal experiments are often used together with PBB absorption models for animal species to gain understanding of drug absorption properties²⁷. Pre-clinical species might offer an opportunity as a fast and time-efficient method to identify potential clinical dosage forms in early development phases or when significant changes in the formulation are requested. As long as the physiological conditions and differences are considered, as can be done in the animal PBB models, this can provide information about the absorption characteristics and its limitations and deliver at least a qualitative assessment of the human absorption situation. In the context of regulatory relevant PBBM before submission, the prediction of the drug product characteristics in animals is considered to be of minor importance as soon as human data are available.

As the drug product's *in vivo* performance is mainly determined by its dissolution behaviour in the GI-tract, an initial PBB absorption model which is focused on solubility, dissolution and permeation might be enough for *in vivo* characterization of the drug formulations. Post-absorption processes like distribution, metabolism and excretion (DME) have typically no relevance for the dosage forms performance in the intestine, but are necessary to integrate the absorption profile into the overall systemic exposure enabling a comparison of the simulated and the observed plasma concentration profile for validation purposes of the PBB absorption model²⁸. However, non-linear DME processes like saturable hepatic first pass within the envisaged dose range need a special investigation, if the absorption rates of formulations under investigation are significantly different. Generally, there is an opportunity in the PBBM to only focus on absorption process in the early decision-making process.

A detailed parameter sensitivity analysis to evaluate the drug substance, product and process parameters which most influence the *in vivo* performance helps to establish the margins of a safe space²⁹. The safe space represents boundaries defined by *in vitro* specifications (i.e., dissolution or other relevant drug product quality attributes), within which drug product batches are anticipated to be bioequivalent to one another. This can be mechanistically explained by other factors than dissolution being rate limiting for drug absorption such as permeation or gastric emptying, see Fig. 2. Within this defined safe space changes to the drug substance and drug product (e.g. polymorph, particle size distribution, composition, manufacturing process, etc.) will not have an influence on the *in vivo* performance.

Physicochemical data, which characterize the compound, should be used together with rich *in vitro* dissolution data to establish the PBB model. Information on permeability needs special consideration to be able to define if the absorption of a compound is dissolution or permeability controlled. The model evolves as more data are generated and integrated allowing verification of previous decisions. Such simulation-based decisions might enable acceleration of the programs before availability of *in vivo* data (e.g. relative BA/BE studies).

Figure 2: Possible relationships between dissolution and drug bioavailability (based on Dickinson et al. 2008)³⁰



Beyond the safe space there is the area of IVIVC, where bioavailability in terms of AUC and C_{max} depends on dissolution and shows a correlation. The knowledge of the absorption process is of fundamental importance in defining formulation strategies. If the formulation and its dissolution performance do not influence bioavailability, the focus can be on the manufacturability of the product as long as it remains within the safe-space area. Modern PBBM technologies support PK based development strategies based on the relationship between *in vitro* and *in vivo* performance and allow for PBBM based formulation development strategies within the safe space where quick adaptations to the drug product can be made without affecting the *in vivo* performance.^{31 32}

Applications of PBBM

Existing applications and data demonstrate viability of PBB models and justify their use in accelerated development programs. Some examples are presented in this document.

Use of PBB models as risk mitigation to ensure more predictable bioequivalence study outcomes and potentially reduce the need for critical-path bioequivalence studies.

An example is the bridging of formulation and/or process changes using an *in silico* model in lieu of a human BE study for immediate release “borderline” compounds (i.e. compounds slightly beyond the ICH M9 eligibility criteria for a biowaiver).

PBBM has been used³³ to predict the formulation performance and to define a ‘bioequivalence safe space’ via virtual bioequivalence (BE) simulation. The case study presented below, describes a compound, with clinical PK data in healthy volunteers and patients using capsule and tablet formulations. The potential impact on the PK in patients by varying the tablet *in vitro* dissolution profiles was evaluated.

Case Study

A PBB model was developed for both capsule and tablet formulations using clinical data “top-down” from several studies to set-up, verify and to apply/use the model. Sensitivity analyses were conducted to assess the effect of a tablet batch with slower dissolution kinetics. Virtual BE assessments were conducted. Virtual clinical trials were simulated (N= 25 patients) comparing the tablet batch used in a BE study and new batches with different drug dissolution profiles as drug input (Existing Batch with measured 98% dissolved at 45 min and Virtual Batch with assumed 80% dissolved at 45 min and less than 80% at 30 min).

The PK simulations suggest that the compound's absorption kinetics is not limited by its solubility and dissolution of the tablet in the gut, but rate-controlled by its moderate permeability. The simulation results indicate that a tablet with 80% dissolved at 45 min or less than 80% at 30 min at pH 2.0 would not alter the PK of the orally delivered compound in patients. This was consistent with similar PK between the capsule and tablet observed in healthy volunteers (capsule vs tablet BE batch) and in patients (capsule vs tablet commercial batch).

A bioequivalence 'safe space' was successfully established, linking *in vitro* with *in vivo* data, i.e. between dissolution data and clinical data. Using PBBM, slight changes in the *in vitro* dissolution of the tablet are not expected to affect the *in vivo* absorption kinetics (rate or extent) and the overall PK profile. This case study exemplifies a path to achieve an *in vitro/in vivo* link toward development of biopredictive dissolution methods to support BE biowaivers.

Other Applications

Another example demonstrates that a weakly basic compound with pH-dependent solubility quickly dissolves in the stomach but stays dissolved in the intestine without precipitation due to a high solubility in the intestinal fluids. This was demonstrated for etoricoxib IR tablets by PBBM³⁴ and verified by a BE study³⁵. Therefore, the fast dissolution process in the stomach is critical for the *in vivo* performance and results in a permeation controlled absorption.

Based on those PBBM results, the product development can be continued simultaneously to the preparation of a confirmatory BE study using two formulations with different dissolution rates in case of slight changes in e.g. manufacturing process and site, PSD specification and minor changes in composition. This approach prevents a delay in development as the formulation related decisions are based on the permeation-controlled absorption determined by PBBM.

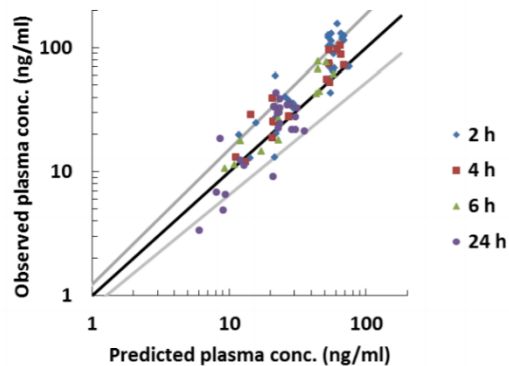
Use of PBB models to guide pediatric formulation development and accelerate the start of clinical studies in pediatric patients

An example for the development of an oral solution of a weak base with strong pH dependent solubility and good oral permeability for use in pediatrics was described by Cordula Stillhart et al.³⁶ An oral absorption model was developed and verified with adult PK data obtained from Phase 1 studies. Fast and complete drug absorption in adults with no precipitation, although significant supersaturation was expected in intestinal fluid, was predicted by the model and confirmed with a two-stage *in vitro* dissolution test.

After scaling down the model to newborns, no significant impact of precipitation time, permeability, dose volume, bile salts solubilization ratio, and stomach/duodenum pH on the total fraction absorbed was predicted. However, some precipitation was anticipated in the newborn intestine when assuming reduced bile salts concentration.

A modified two-stage *in vitro* dissolution test simulating reduced concentrations of bile fluids and higher stomach pH in infants confirmed very stable solution, suggesting that the predicted *in vivo* precipitation was unlikely. Similarly, no influence of formulation excipients on the solubilization behavior was observed.

Based on these findings it was concluded that the oral absorption behaviour in adults and pediatric age groups is similar and no formulation effects were expected (minor adaptation of formulation between Phase 1 and 2/3). Therefore, infants were dosed in the pediatric study without a previous bioavailability study. Later on, the pediatric model was verified with PK data obtained from 33 infants (< 1 year old) and confirmed accurate PK predictions.



Use of PBB models to support control strategy related to specification setting for particle size distribution (PSD) and dissolution and selection of dissolution method based on limited data with the commercial process/formulation.

An example of this application is described in 'Physiologically Based Absorption Modelling to Predict the Impact of Drug Properties on Pharmacokinetics of Bitopertin'.³⁷ The model predicted differences in *in vivo* bioavailability depending on particle size and was used for intrapolation and estimation of an appropriate particle size specification for a BCS Class II drug.

A further example is described by Pepin *et al.* (2016).³⁸ In this example, PBB absorption modelling was used in combination with clinical relative bioavailability data to define a dissolution safe space and underpin the dissolution and particle size specifications at time of registration. This approach was accepted by US FDA.

Use of PBB models to inform design of a second generation formulation fast-following commercial launch with a prototype/clinical formulation.

In silico models are valuable in the development of a second generation formulation to improve patient convenience (e.g. taste masking) and compliance. Depending on the characteristics of the drug substance and drug product and the extent of formulation changes, it would be possible to use these models to bridge a new formulation for a line extension application instead of executing a human study. Kesioglou *et al.*³⁹ present several cases related to studying the impact of formulation properties on the *in vivo* performance *via* absorption modelling, and the use of this information to guide robust formulation development. The examples presented span early and late development stages and include both immediate- and controlled-release dosage forms.

Mitra *et al.*⁴⁰ present two case studies illustrating how *in vitro* dissolution profiles in absorption models can be used to predict bioequivalence of immediate- and controlled-release products.

Use of PBB absorption models to predict the effect of food and drug interactions due to changed gastric pH

Clinically relevant drug interactions may be caused when drugs with pH-dependent solubility are co-administered with gastric acid reducing agents and so considerable efforts are taken during drug development to mitigate pH-dependent Drug-Drug Interactions (DDIs) and regulators may require clinical assessment. PBBM can play a prominent role in mechanistic understanding of pH-dependent DDIs and recent work has demonstrated that a wider application to streamline drug development and waive unnecessary studies is warranted (Mitra et al, 2020. Parrott 2016).^{41 42 43}

Physiologically based modelling of food effects is also used widely within the pharmaceutical industry with numerous examples available in the literature. Although a thorough verification of a generic food effect modelling approach remains to be achieved⁴⁴, examples have demonstrated the potential of the approach to extrapolate from one formulation to another and from one meal type to another⁴⁵ and to predict the effect of dose administration timing with respect to meals. A recent cross-company publication has proposed a strategy for implementation in drug development leading to regulatory impact (Tistaert 2019).⁴⁶

Agile and information rich *in vivo* study designs

As described earlier in this paper, the opportunity afforded by accelerated development and registration brings corresponding pressure on the development and optimisation of the drug product. The compressed development timelines mean that the traditional approach to studying formulation changes in the clinic (i.e. a linear approach where a relative bioavailability study is performed on an optimised formulation composition prior to clinical dose setting and manufacture of clinical batches) is highly unlikely to be feasible. Furthermore, for some oncology products (which are often the subject of accelerated developments due to the high unmet medical need in this area), dosing to healthy volunteers is either not possible due to the genotoxic nature of the API, or is only permitted at doses much lower than the highest clinical dose. Performing bioequivalence studies in patients typically takes much longer due to recruitment difficulties. A more agile approach to formulation optimisation and to characterising clinical formulation performance is therefore warranted for accelerated developments. Proactive design of the clinical pharmacology plan, including conscious integration with the evolving *in vitro* and *in silico* models, can provide opportunities to proceed more confidently with formulation changes later in the clinical plan, avoiding the need for relative bioavailability or BE studies on the critical path. Specific opportunities in this area are highlighted below.

Opportunity: use of adaptive design studies for rapid formulation development

Adaptive designs can be used for rapid formulation selection and optimisation based on clinical data. Zann et al. describe the use of such a study for ME-401, a PI3K inhibitor.⁴⁷ As part of the first-in-human trial, several formulation approaches were assessed to identify the most appropriate formulation approach to take into patient studies, and subsequent cohorts were used for optimisation of the selected formulation (e.g. to increase drug loading). A flexible study design was employed, with real-time PK analysis to facilitate decision making between cohorts based on emerging data.

Utility in accelerated development: rapid development of qualitative formulation for pivotal studies based on human data.

Opportunity: establish product-specific *in vivo/in vitro* understanding to bridge future changes

The concept of clinically relevant dissolution tests and specifications has been widely discussed in recent years among industry and regulators, including a recent industry White Paper and an M-CERSI workshop.^{48 49 50 51 52 53 54} This approach is underpinned by a clinical relative bioavailability study, in which process and formulation variants with different *in vitro* dissolution profiles are administered and the impact on *in vivo* drug product performance is assessed. This enables the relationship between *in vitro* dissolution and *in vivo* performance to be defined on a drug product specific basis, so that the impact of future changes (e.g. to manufacturing process parameters) can be evaluated without the need for further clinical studies. These data can be augmented by developing *in silico* PBB absorption models to provide enhanced mechanistic insight.

Utility in accelerated development: Could enable later scale-up activities to be performed without the need for *in vivo* BE (based on the understanding and models developed), thus saving time and enabling commercial scale product to be dosed to patients more quickly. Notably, this approach enables *in vivo/in vitro* relationship to be established for a wider range of circumstances than the current IVIVC guidelines.

Opportunity: clinical studies providing mechanistic insight into critical factors for absorption

Clinical relative bioavailability studies can be augmented with markers for aspects of GI physiology that can affect absorption. This provides mechanistic insight into critical factors affecting absorption, and enables the development of improved *in silico* absorption models by separating the 'noise' from physiological variability from product performance⁵⁵. *In vivo* tools that can support this approach include:

- Smart Pills ® to measure gastric pH and pressure⁵⁶
- Salivary measurement of paracetamol pharmacokinetics to characterize gastric emptying⁵⁷
- High resolution manometry for shear forces⁵⁸
- Magnetic marker monitoring for *in vivo* dosage form disintegration⁵⁹

Pepin *et al.*³⁸ developed a mechanistic PBB absorption model for Lesinurad, including customization for individual disposition parameters and gastric emptying times, which was used to justify drug product specifications in the US marketing application. Incorporation of accurate gastric pH was also shown to be a critical parameter in the *in silico* PBBM predictions for acalabrutinib⁶⁰.

Utility in accelerated development: Understand the factors underlying pharmacokinetic variability, enabling the design of drug products with more optimal performance in the patient and the validation of *in vitro* and *in silico* tools to predict the impact of changes to drug product attributes. Enable product performance in the wider patient population to be more accurately predicted, by adjusting critical physiological parameters in the model to the extremes known to occur in the patient group (e.g. virtual BE trials in an *in silico* patient population).

In conclusion, accelerated developments necessitate a different approach to formulation development, optimisation and bridging to ensure that patients can benefit from optimised drug products. Agile and information-rich clinical study designs can be valuable in this setting to develop formulation understanding and underpin the development of *in vitro* and *in silico* models, to support flexible bridging approaches that go beyond the current regulatory guidelines based on deep product-specific mechanistic knowledge.

Conclusions

This White Paper has been developed to illustrate some opportunities and applications of biopharmaceutics models to support accelerated patient access to innovative medicines by reducing the overall time required to develop a robust high-quality drug product with the desired clinical performance. Industry believes that a deep understanding of fundamental biopharmaceutics properties of the active substance and product and the application of biopharmaceutics models are powerful tools in the acceleration of development programs.

This paper illustrates examples of applications of various biopharmaceutics models such as bio-relevant *in vitro* systems and tools, *in silico* PBBM, and agile and information rich *in vivo* study designs. The application of these tools can support accelerated access and sustained supply of medicines developed under accelerated programs.

There is an opportunity to move beyond traditional BCS thinking to understand *in vitro/in vivo* relationship on a product-specific basis, to enable the establishment of clinically relevant *in vitro* tests and acceptance criteria. This, in combination with *in silico* modelling, can be used to facilitate rapid product and process development, with optimisation and scale up based on knowledge of the potential *in vivo* impact of any changes, and ultimately to define the control strategy to ensure that drug product of suitable clinical quality is always delivered.

The discussion in this manuscript has focused on small molecule APIs administered as oral immediate release dosage forms, as this is the subject of many of the published examples. However, it should be emphasized that the same scientific principles of biopharmaceutics risk assessment can be applied to other drug product types and routes of administration, and indeed the generation of this knowledge and understanding would be equally necessary and useful to support accelerated development for these product types. The biorelevant *in vitro* methods and *in silico* models for these product types may be less well evolved than for the oral route and therefore would require more product-specific verification, thereby placing increased emphasis on the use of information-rich *in vivo* studies for these formulations.

The topics of biorelevant dissolution and PBBM were discussed in depth at the FDA M-CERSI workshop in September 2019. Both FDA and EMA presented their view on the opportunities and use of Physiologically Based Biopharmaceutics Modeling to build a safe space to gain regulatory flexibility while assuring consistent *in vivo* product performance for the marketed product relative to the clinical trial formulation and ultimately that every dose is safe and effective^{61 62 63}

We believe that continued scientific engagement and close collaboration between the Regulators and the Industry will be key to support the development of a harmonized, science-based global position on the application of these tools. This would represent an opportunity to unleash the potential of the existing biopharmaceutics tools and transform them into a powerful scientific and regulatory tool to support acceleration of technical development and early patient access to new innovative drugs.

Abbreviations

API: Active Pharmaceutical Ingredient

BCS: Biopharmaceutics Classification System

BA: Bioavailability

BE: Bioequivalence

CMC: Chemistry, Manufacturing and Controls

DDI: Drug-Drug Interaction

DME: Distribution, Metabolism and Excretion

IMI: Innovative Medicines Initiative

IPD: *In vivo* Predictive Dissolution

IR: Immediate Release

IV: Intravenous

IVIVC: *In vitro in vivo* correlation

M-CERSI: Maryland Center for Excellence in Regulatory Science and Innovation

OrBiTo: ORal Biopharmaceutics TOols

PBBM: Physiologically-Based Biopharmaceutics Modeling

PK: Pharmacokinetic

PRIME: PRiority Medicines

PSD: Particle Size Distribution

TNO-TIM1: TNO (Gastro-) Intestinal Model

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